FIG. 1

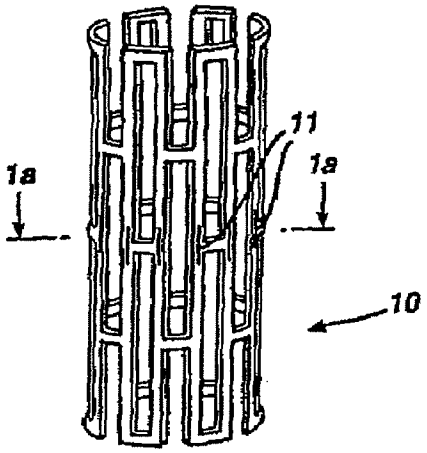


FIG. 1a

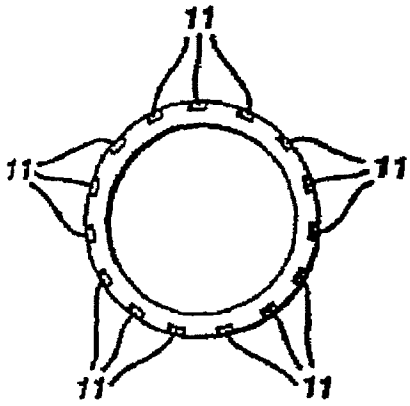


FIG. 2a

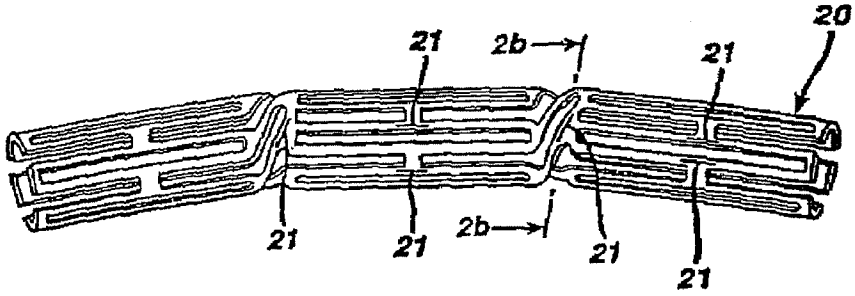


FIG. 2b

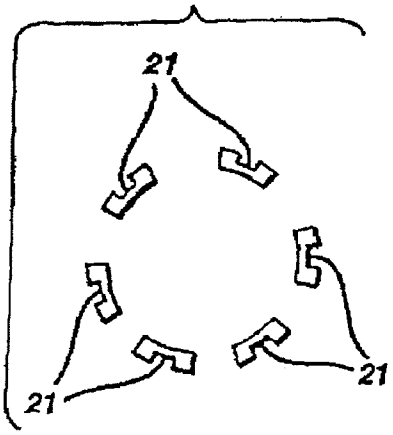


FIG. 3a

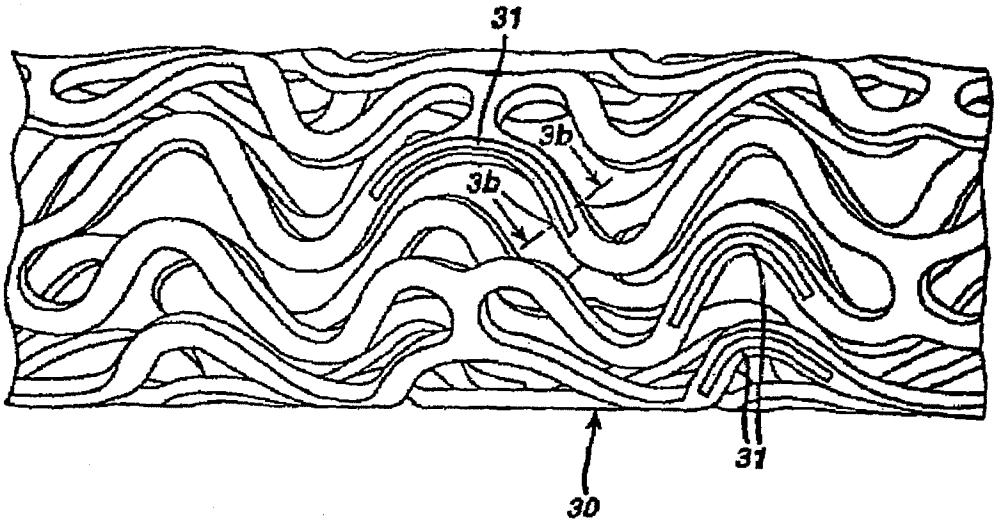


FIG. 3b

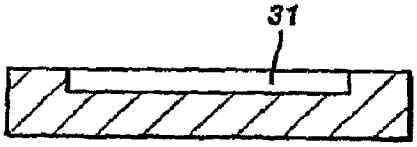
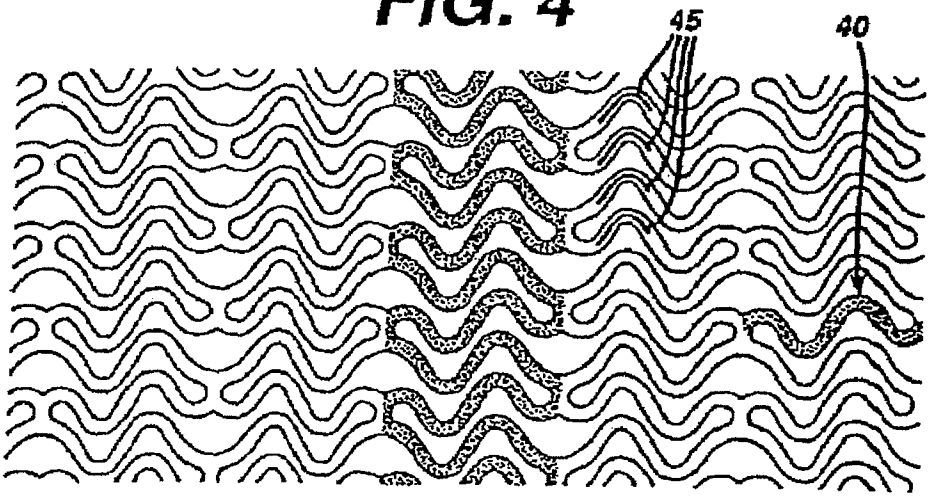


FIG. 4



LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of Ser. No. 10/951,385, filed Sep. 28, 2004, now pending, which is a continuation of Ser. No. 10/408,328, filed Apr. 7, 2003, now issued as U.S. Pat. No. 6,808,536, which is a continuation of application Ser. No. 09/874,117, filed Jun. 4, 2001, now issued as U.S. Pat. No. 6,585,764, which is a continuation of application Ser. No. 09/061,568, filed Apr. 16, 1998, now issued as U.S. Pat. No. 6,273,913, which in turn claims benefit of provisional application Ser. No. 60/044,692, filed Apr. 18, 1997. The disclosures of these prior applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise althrough the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antinsense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transiuminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified.

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a contractile phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), etc. released from platelets (i.e., PDGF) adhering to the

damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotyope to a synthetic phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: Vascular Smooth Muscle Cells in Culture, Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca. Ratioh, 1987, pp. 39–55); Clowes, A. W. and Schwartz, S. M., Circ. Res. 56:139–145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374–1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30–50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which

FIGS. **1** and **1A** are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. **2***a* and **2***b* are similar views of an alternate embodiment of the stent with open ends;

FIGS. **3***a* and **3***b* are further alternate figures of a device containing a grooved reservoir; and

FIG. **4** is a layout view of a device containing a reservoir as in FIG. **3**.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127–132 (1991); Popma et al., 84 Circulation, 1426–1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 Coronary Artery Disease, 2-32-242 (1993); Serruys, P. W. et al., 88 Circulation, (part 1) 1588–1601, (1993).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent **10** seen in layout in FIG. **4**, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med, 496–501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et

al., 93 Circulation, 412–422, (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 Nature, 25–626, (1977); Guyton, J. R. et al. 46 Circ. Res., 625–634, (1980); Clowes, A. W. and Clowes, M. M., 52 Lab. Invest., 611–616, (1985); Clowes, A. W. and Clowes, M. M., 58 Circ. Res., 839–845 (1986); Majesky et al., 61 Circ Res., 296–300, (1987); Snow et al., 137 Am. J. Pathol., 313–330 (1990); Okada, T. et al., 25 Neurosurgery, 92–898, (1989) colchicine (Currier, J. W. et al., 80 Circulation, 11–66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 Science, 186–188 (1989), angiopeptin (Lundergan, C. F. et al., 17 Am. J. Cardiol. (Suppi. B); 132B–136B (1991), Cyclosporin A (Jonasson, L. et. al., 85 Proc. Nati, Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., 253 Science, 1129–1132 (1991), terbinafine (Nemecek, G. M. et al., 248 J. Pharmacol. Exp. Thera., 1167–11747 (1989), trapidil (Liu, M. W. et al., 81 Circulation, 1089-1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 J. Circulation, 1266–1272 (1991), steroids (Colburn, M. D. et al., 15 J. Vasc. Surg., 510–518 (1992), see also Berk, B. C. et al., 17 J. Am. Coll. Cardiol., 111B–117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G.sub.1 to 5 phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol. Res. 13: 110–116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (Circ Res 76:412–417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277–2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409–1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods: These can vary:

- Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.
- Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.
- or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.
- or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.
- Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake.
- Extravascular delivery by the pericardial route.
- Extravascular delivery by the advential application of sustained release formulations.

Uses:

- for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.
- prevention of tumor expansion from stents.
- prevent ingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides; poly-amino acids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any

identified in the first experimental method, is applied to the stent as detailed above. This outer layer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery via Lysis of a Covalent Drug Tether:

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery:

A: Polymeric Sheet

Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-gylcolid-e) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10.mu. to 1000.mu. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating:

Rapamycin is combined with a polymer that has a melting temperature just above 37° C., range 40°–45° C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformably to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. **1***a*, **2***a* and **3***a*, any stent strut **10**, **20**, **30** can be modified to have a certain reservoir or channel **11**, **21**, **31**. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut. Of course, this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed:

1. A metallic stent having a coating applied thereto, wherein:

said coating comprises a mixture of a biocompatible polymeric carrier and a therapeutic agent;

said polymeric carrier comprises at least one nonabsorbable polymer;

said therapeutic agent is rapamycin, or a macrocyclic lactone analog thereof, present in an amount effective to inhibit neointimal proliferation; and

said stent provides a controlled release of said therapeutic agent over a period of several weeks.

2. The metallic stent according to claim **1** wherein said therapeutic agent is a macrocyclic lactone analog of rapamycin.

3. The metallic stent according to claim **1** wherein said biocompatible polymeric carrier comprises a fluorinated polymer.

4. The metallic according to claim **3** wherein said biocompatible polymeric carrier further comprises an acrylate-based polymer or copolymer.

5. A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting a metallic stent according to any one of claims **1** to **4** in the lumen of said coronary artery.

* * * * *

(12) **United States Patent**
Roorda et al.

(10) **Patent No.: US 7,247,313 B2**
(45) **Date of Patent: *Jul. 24, 2007**

(54) **POLYACRYLATES COATINGS FOR IMPLANTABLE MEDICAL DEVICES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 177 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/176,504**

(22) Filed: **Jun. 21, 2002**

(65) **Prior Publication Data**

US 2005/0106203 A1 May 19, 2005

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/894,293, filed on Jun. 27, 2001, now abandoned.

(51) **Int. Cl.**
A61F 2/02 (2006.01)
A61K 9/00 (2006.01)

(52) **U.S. Cl.** **424/423**; 424/426; 424/400

(58) **Field of Classification Search** 424/423, 424/422, 400, 426; 623/1.16, 1.42
See application file for complete search history.

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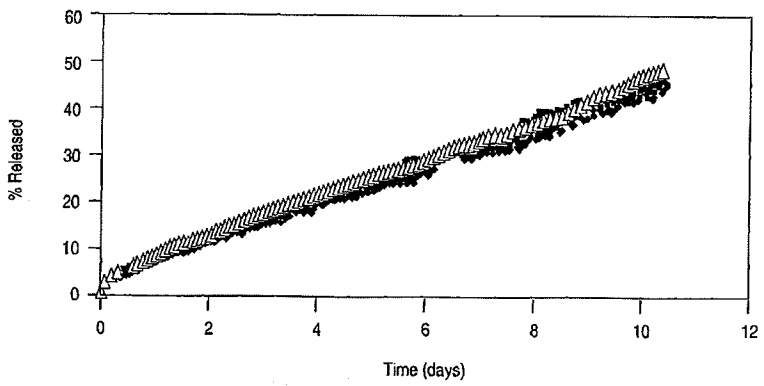
Primary Examiner—Michael G. Hartley
Assistant Examiner—Blessing Fubara
(74) *Attorney, Agent, or Firm*—Squire, Sanders & Dempsey L.L.P.

(57) **ABSTRACT**

A coating for a medical device, particularly for a drug eluting stent, is described. The coating can include a polyacrylate, a blend of polyacrylates, or a blend of the polyacrylate with other polymers, for example, poly(ethylene-co-vinyl alcohol).

21 Claims, 2 Drawing Sheets



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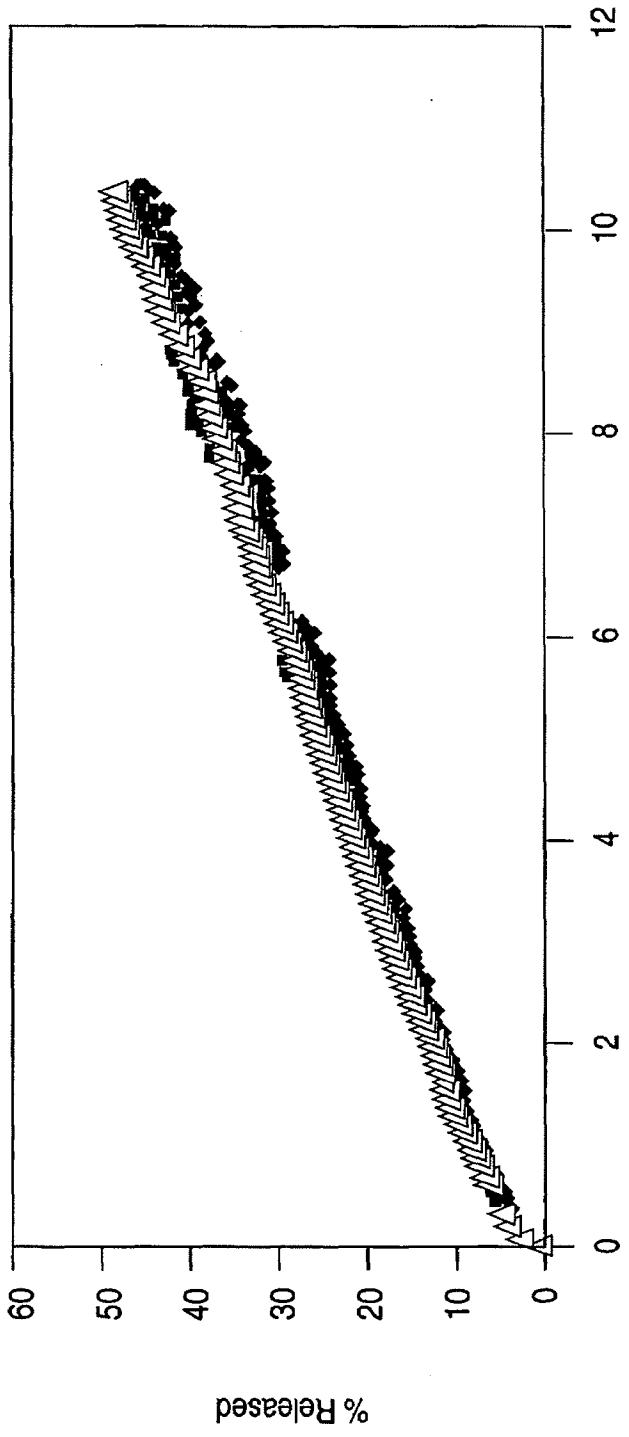

FIG. 1

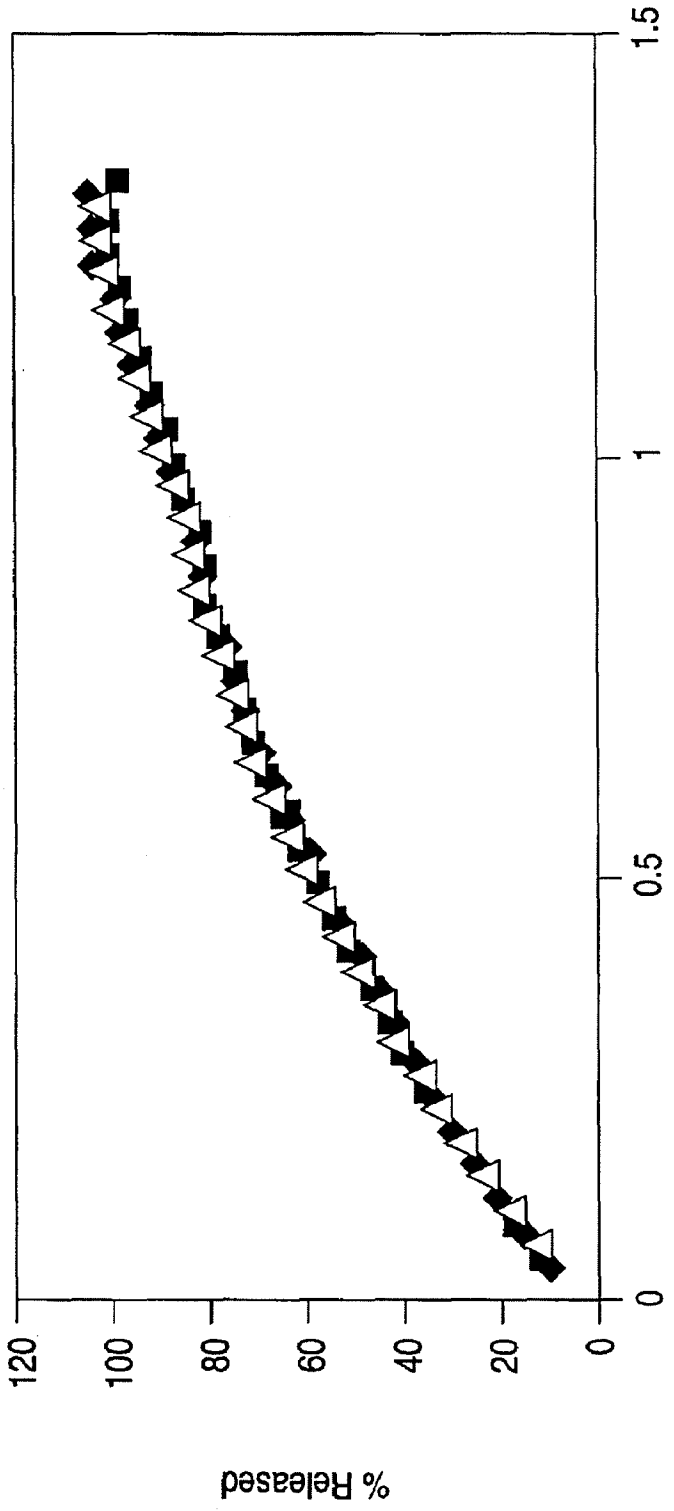

FIG. 2

POLYACRYLATES COATINGS FOR IMPLANTABLE MEDICAL DEVICES

CROSS REFERENCE

This is a continuation-in-part of U.S. patent application Ser. No. 09/894,293, filed on Jun. 27, 2001, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention is directed to coatings for implantable medical devices, such as drug eluting vascular stents.

2. Description of Related Art

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially compress against the atherosclerotic plaque of the lesion to remodel the lumen wall. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of intimal flaps or torn arterial linings which can collapse and occlude the conduit after the balloon is deflated. Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, a stent is implanted in the lumen to maintain the vascular patency.

Stents are used not only as a mechanical intervention but also as a vehicle for providing biological therapy. As a mechanical intervention, stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically, stents are capable of being compressed, so that they can be inserted through small vessels via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in patent literature disclosing stents which have been applied in PTCA procedures include stents illustrated in U.S. Pat. No. 4,733, 665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco, and U.S. Pat. No. 4,886,062 issued to Wiktor.

Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results. One proposed method for medicating stents involves the use of a polymeric carrier coated onto the surface of a stent. A solution which includes a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent. The solvent is allowed to evaporate, leaving on the stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer. The embodiments of the invention provide coatings for implantable devices, such as stents, and methods of coating the same.

SUMMARY

A coating for an implantable medical device is provided, the coating comprises a thermoplastic polyacrylate material free from acetate species and a therapeutically active agent incorporated therein. The polyacrylate material can include homopolymers, copolymers or terpolymers of alkylacrylates or alkylmethacrylates, and blends thereof. The polyacrylate material can be poly(n-butyl methacrylate). The polyacrylate material can include non-acrylate polymers such as fluorinated polymers or poly(ethylene-co-vinyl alcohol).

According to another embodiment of this invention, a coating for an implantable medical device is provided, the coating comprises a first layer having an active agent incorporated therein and a second layer disposed over the first layer, wherein the second layer comprises a thermoplastic polyacrylate material for modifying the rate of release of the agent.

According to yet another embodiment of the invention, a method of coating an implantable medical device is provided, the method comprises depositing a first layer on the device, the first layer including an active agent for the sustained release of the agent, and depositing a second layer over the first layer, the second layer comprising a thermoplastic polyacrylate material for modifying the rate of release of the agent.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1** and **2** are graphs illustrating a profile of a rate of release of a drug from stents coated according to a method of the present invention.

DETAILED DESCRIPTION

A coating for an implantable medical device, such as a stent, according to one embodiment of the present invention, can include a drug-polymer layer, an optional topcoat layer, and an optional primer layer. The drug-polymer layer can be applied directly onto the stent surface to serve as a reservoir for a therapeutically active agent or drug which is incorporated into the drug-polymer layer. The topcoat layer, which can be essentially free from any therapeutic substances or drugs, serves as a rate limiting membrane which further controls the rate of release of the drug. The optional primer layer can be applied between the stent and the drug-polymer layer to improve the adhesion of the drug-polymer layer to the stent.

According to one embodiment of the present invention, polymers of esters having the general formula (I)

$$-[CH_2-C(X)(COOR)]_m-[CH_2-C(X')(COOR')]_n-[CH_2-C(X'')(COOR'')]_p-, \quad (I)$$

or blends thereof, can be used for making the stent coatings.

In formula (I), X, X', and X" is each, independently, a hydrogen atom (acrylates) or an alkyl group, such as a methyl group CH_3 (methacrylates); R, R' and R" is each, independently, a C_1 to C_{12} straight chained or branched aliphatic radical; "m" is an integer larger than 1, and "n" and "p" is each 0 or an integer. If both n=0 and p=0, the polymer of formula (I) is a homopolymer (i.e., PBMA). If n≠10 and

p=0, or n=0 and p≠0, the polymer of formula (I) is a copolymer, and if n≠0 and p≠0, the polymer of formula (I) is a terpolymer.

Polymers of formula (I) can be used for making either the drug-polymer layer, the topcoat membrane, the optional primer layer, or any combination thereof. For the purposes of the present invention, such polymers, or blends thereof, are defined as "polyacrylates" or as "polyacrylate materials."

One example of a polyacrylate suitable for fabricating either the drug-polymer layer or the topcoat membrane is poly(n-butyl methacrylate) (PBMA), described by formula (I) where X=CH_3, n=0, p=0, and "R" is a n-butyl radical C_4H_9 (—CH_2—CH_2—CH_2—CH_3). PBMA has good biocompatibility, is soluble in many common solvents, has good mechanical and physical properties, and adheres well to the underlying stent surface or the primer layer. PBMA is available commercially from Aldrich Chemical Co. of Milwaukee, Wis., and from Esschem, Inc. of Lynwood, Pa.

The rate of release of the drug through the polymer, such as the topcoat membrane, is related to the rate of diffusion of the drug through the matrix. The slower the rate of diffusion, the greater the polymer's ability to prolong the rate of release and the residence time of the drug at the implantation site. The rate of diffusion is in turn related to the water adsorption rate, the degree of crystallinity, if any, and the glass transition temperature (T_g) of the polymer.

As a general rule, the more water the polymer absorbs at body temperature, the faster the drug diffuses out of the polymer, and the greater the degree of crystallinity in the polymer's structure, the slower a drug will diffuse out of the polymer. Since all of the R, R' and R" groups in these polyacrylates are aliphatic, water adsorption tends to be low. One common technique for producing these polymers is by free radical polymerization yielding amorphous polymers with no crystallinity. Hence, it is the glass transition temperature that is one of the important discriminating characteristic for these polymers.

Consequently, the present invention allows manipulating the rate of release of the drug into the blood stream by varying T_g of the polymer or the blend of polymers forming the drug-polymer layer and/or the membrane. Typically, it is desirable to decrease the rate of release. In order to do so, the polyacrylates having higher values of T_g can be used. Examples of such polyacrylates include poly(methyl methacrylate) (T_g=105° C.) and poly(tert-butyl methacrylate) (T_g=107° C.).

However, if it is desirable to increase the rate of release, the polyacrylates having low values of T_g can be used.

PBMA is one of such polyacrylates having the T_g of about 20° C. Examples of other suitable polyacrylates having low T_g include poly(n-hexyl methacrylate) (T_g=-5° C.) and poly(methyl acrylate) (T_g=9° C.).

For a copolymer of these polyacrylates, the Tg (on the Kelvin scale) is generally the mass-fraction weighted average of the constituent components of the copolymer. Consequently, a copolymer or terpolymer of formula (I) with predetermined higher or lower value of T_g can be used as a drug-polymer layer and/or a topcoat membrane, thus providing a desirable lower or higher rate of release of the drug, respectively. For example, a random poly(methyl methacrylate-co-n-butyl methacrylate) [P(MMA-BMA)], having about 30 molar percent of methyl-methacrylate-derived units and about 70 molar percent of n-butyl-methacrylate-derived units, has a theoretical T_g of about 45.50° C. Therefore, a topcoat membrane made of P(MMA-BMA) will provide faster drug release than pure PMMA but slower than pure PBMA. Similarly, blends of individual polyacrylates, e.g., PBMA and PMMA can be used.

Some examples of polyacrylates that are suitable for fabrication of the coating, e.g., the drug-polymer layer and/or the topcoat membrane, are summarized in Table 1.

TABLE 1

Examples of Polyacrylates —[CH_2—C(X)(COOR)]$_m$—[CH_2—C(X')(COOR')]$_n$— Suitable for Fabricating Stent Coatings

No.	Polyacrylate	Abbreviation	R	X	m	R'	X'	n	T_g, ° C.
1	Poly(n-butyl methacrylate)	PBMA	i-C_4H_9	CH_3	>1	N/A	N/A	0	20
2	Poly(iso-butyl methacrylate)	Pi-BMA	i-C_4H_9	CH_3	>1	N/A	N/A	0	66
3	Poly(tert-butyl methacrylate)	PBMA	tert-C_4H_9	CH_3	>1	N/A	N/A	0	107
4	Poly(methyl methacrylate)	PMMA	CH_3	CH_3	>1	N/A	N/A	0	105
5	Poly(ethyl methacrylate)	PEMA	C_2H_5	CH_3	>1	N/A	N/A	0	63
6	Poly(n-propyl methacrylate)	PPMA	n-C_3H_7	CH_3	>1	N/A	N/A	0	35
7	Poly(methyl acrylate)	PMA	CH_3	H	>1	N/A	N/A	0	9
8	Poly(n-hexyl methacrylate)	PHMA	n-C_6H_{13}	CH_3	>1	N/A	N/A	0	-5
9	Poly(methyl methacrylate-co-n-butyl methacrylate)	P(MMA-BMA)	CH_3	CH_3	30	n-C_4H_9	CH_3	70	46
10	Poly(n-butyl methacrylate-co-iso-butyl methacrylate)	P(BMA-i-BMA)	n-C_4H_9	CH_3	50	i-C_4H_9	CH_3	50	35

Only homo- and copolymers are listed in Table 1 (that is, the polymers of formula (I) where p=0), but it should be understood that terpolymers corresponding to formula (I) (when n≠0 and p≠0) can be used as well.

To fabricate the coating, one of the polyacrylates, or a blend thereof can be applied on the stent using commonly used techniques known to those having ordinary skill in the art. For example, the polyacrylate can be applied to the stent by dissolving the polymer in a solvent, or a mixture of solvents, and applying the resulting solution on the stent by spraying or immersing the stent in the solution.

Representative examples of some suitable solvents include N,N-dimethylacetamide (DMAC), N,N-dimethylformamide (DMF), tethrahydrofurane (THF), cyclohexanone, xylene, toluene, acetone, methyl ethyl ketone, propylene glycol monomethyl ether, methyl butyl ketone, ethyl acetate, n-butylacetate, and dioxane. Examples of suitable mixtures of solvents include mixtures of DMAC and methanol (e.g., a 50:50 by mass mixture), cyclohexanone and acetone (e.g., 80:20, 50:50, 20:80 by mass mixtures), acetone and xylene (e.g. a 50:50 by mass mixture), and acetone, FLUX REMOVER AMS, and xylene (e.g., a 10:50:40 by mass mixture). FLUX REMOVER AMS is trade name of a solvent manufactured by Tech Spray, Inc. of Amarillo, Tex. comprising about 93.7% of a mixture of 3,3-dichloro-

1,1,1,2,2-pentafluoropropane and 1,3-dichloro-1,1,2,2,3-pentafluoropropane, and the balance methanol, with trace amounts of nitromethane.

In addition, blends of polyacrylates with polymers other than polyacrylates can be used to fabricate the coating. In one embodiment, the blend of polyacrylates with non-acrylate materials is free from acetate species. Poly(ethylene-co-vinyl alcohol) (EVAL) is one example of a suitable non-acrylate polymer. EVAL has the general formula $—[CH_2—CH_2]_q—[CH_2—CH(OH)]_r—$, where "q" and "r" is each an integer. EVAL may also include up to 5 molar % of units derived from styrene, propylene and other suitable unsaturated monomers. A brand of copolymer of ethylene and vinyl alcohol distributed commercially under the trade name EVAL by Aldrich Chemical Co., or manufactured by EVAL Company of America of Lisle, Ill., can be used.

Examples of other polymers with which polyacrylates can be blended include fluorinated polymers, such as poly(vinylidene fluoride) (PVDF) and poly(vinylidene fluoride-co-hexafluoro propene) (PVDF-HFP). The blend of a polyacrylate and a fluorinated polymer can contain between about 10 and about 95% (mass) of the fluorinated polymer.

The polyacrylates can be used to manufacture the primer layer, drug-polymer layer, topcoat membrane, or all three layers. For example, the polyacrylates can be used to make both the drug-polymer layer and the topcoat membrane, but not the primer layer. Any combination of the three layers can include a polyacrylate, so long as at least one of the layers includes the material. If a polyacrylate is used to make only one of the layers, the other layer or layers can be made of an alternative polymer.

Representative examples of suitable alternative polymers include EVAL, poly(hydroxyvalerate), poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane; poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), co-poly(ether-esters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes, biomolecules (such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid), polyurethanes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, acrylic polymers and copolymers other than polyacrylates, vinyl halide polymers and copolymers (such as polyvinyl chloride), polyvinyl ethers (such as polyvinyl methyl ether), polyvinylidene halides (such as polyvinylidene fluoride and polyvinylidene chloride), polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics (such as polystyrene), polyvinyl esters (such as polyvinyl acetate), acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers), polyamides (such as Nylon 66 and polycaprolactam), alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, and carboxymethyl cellulose.

The coating of the present invention has been described in conjunction with a stent. However, the coating can also be used with a variety of other medical devices. Examples of the implantable medical device, that can be used in conjunction with the embodiments of this invention include stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, axius coronary shunts and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt-chromium alloys (e.g., ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, tantalum-based alloys, nickel-titanium alloy, platinum, platinum-based alloys such as, e.g., platinum-iridium alloy, iridium, gold, magnesium, titanium, titanium-based alloys, zirconium-based alloys, or combinations thereof. Devices made from bioabsorbable or biostable polymers can also be used with the embodiments of the present invention.

"MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co. of Jenkintown, Pa. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum.

The active agent or the drug can include any substance capable of exerting a therapeutic or prophylactic effect for a patient. The drug may include small molecule drugs, peptides, proteins, oligonucleotides, and the like. The active agent could be designed, for example, to inhibit the activity of vascular smooth muscle cells. It can be directed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells to inhibit restenosis. Examples of drugs include antiproliferative substances such as actinomycin D, or derivatives and analogs thereof. Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel, docetaxel, methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin, hydrochloride, and mitomycin. Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin. Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril, cilazapril or lisinopril, calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (ω-3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon; genetically engineered epithelial cells; rapamycin and structural derivatives or functional analogs thereof, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of Everolimus available from Novartis) 40-O-(3-hydroxy)propyl-rapamycin and 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin; tacrolimus; and dexamethasone.

EXAMPLES

Some embodiments of the present invention are illustrated by the following Examples.

Example 1

A polymer solution containing between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of EVAL and the balance, DMAC solvent, can be prepared. The solution can be applied onto a stent to form a primer layer. To apply the primer layer, a spray apparatus, such as an EFD 780S spray nozzle with a VALVEMATE 7040 control system, manufactured by EFD, Inc. of East Providence, R.I. can be used. The EFD 780S spray nozzle is an air-assisted external mixing atomizer. The composition is atomized by air and applied to the stent surfaces. During the process of applying the composition, the stent can be optionally rotated about its longitudinal axis, at a speed of 50 to about 150 rpm. The stent can also be linearly moved along the same axis during the application.

The EVAL solution can be applied to a 13-mm TETRA stent (available from Guidant Corporation) in a series of 10-second passes, to deposit, for example, 10 μg of coating per spray pass. Instead of the 13-mm TETRA stent, another suitable stent can be used, for example, a 12-mm VISION stent (also available from Guidant Corporation). Between the spray passes, the stent can be dried for about 10 seconds using flowing air with a temperature of about 60° C. Five spray passes can be applied, followed by baking the primer layer at about 140° C. for one hour. As a result, a primer layer can be formed having a solids content of about 50 μg. "Solids" means the amount of the dry residue deposited on the stent after all volatile organic compounds (e.g., the solvent) have been removed.

A drug-containing formulation can be prepared comprising:

(a) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of EVAL;

(b) between about 0.1 mass % and about 2 mass %, for example, about 1.0 mass % of an active agent, for example, Everolimus; and

(c) the balance, a solvent mixture of DMAC and pentane, the solvent mixture containing about 80 (mass) % of DMAC and about 20 (mass) % of pentane.

In a manner identical to the application of the primer layer, five spray passes can be performed, followed by baking the drug-polymer layer at about 50° C. for about 2 hours, to form the drug-polymer layer having a solids content between about 30 μg and 750 μg, for example, about 90 μg, and a drug content of between about 10 μg and about 250 μg, for example, 30 μg.

Finally, a topcoat composition to control the drug release rate can be prepared, comprising between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % PBMA and the balance a solvent system, for example, a solvent system including a 10:50:40 (mass) blend of acetone, Techspray's FLUX REMOVER AMS, and xylene. In a manner identical to the application of the primer layer and the drug-polymer layer, a number of spray passes are performed followed by final baking at about 50° C. for about 2 hours. As a result, the topcoat membrane can be formed, the membrane having a solids content of between about 30 μg and about 350 μg, for example, about 50 μg.

Example 2

A stent was coated as described in Example 1, except instead of the Everolimus, estradiol was used. The coated stent was tested for a study of the drug release. The stent was immersed for 24 hours in bovine serum. The drug was extracted, and the amount of estradiol released after 24 hours was measured chromatographically (by HPLC). The results of this study are summarized in Table 2.

TABLE 2

Drug Release Study of Stent Coatings Having PBMA Topcoat Membranes (EVAL-based Drug-Polymer Layer, Estradiol Drug)

No.	Topcoat Membrane Solids, μg	Drug Loaded in the Drug-Polymer Layer, μg	% of the Drug Released in 24 Hours
1	30	240	15.0
2	50	240	13.0
3	100	240	11.0
4	160	240	4.3
5	300	170	1.5

Further, a kinetic study of the drug release profile was conducted. The stent had the total amount of solids of the topcoat membrane of about 160 μg and the total amount of estradiol in the drug-polymer layer of about 30 μg. The stent was immersed in a phosphate buffered saline solution having 1 mass % of sodium dodecyl sulfate. A sample of the solution was taken every 20 minutes and analyzed by HPLC for the amount of estradiol released.

As seen from the release profile for three different coated stents shown on FIG. 1, after 10 days about 50 mass % of estradiol was released in an almost perfect linear profile indicating a topcoat layer-controlled zero-order type of release. The small burst in the first 24 hours is due to the saturation of the topcoat layer with the drug. Once a stable state was established, the release rate remained constant for 240 hours. The linear correlation coefficient between 24 and 240 hours was 0.997.

Example 3

A stent was coated as described in Example 1, except instead of Everolimus, etoposide was used. The coated stent was tested for a study of the drug release as described in Example 2. The results of this study are summarized in Table 3.

TABLE 3

Drug Release Study of Stent Coatings Having PBMA Topcoat Membranes (EVAL-based Drug-Polymer Layer, Etoposide Drug)

No.	Topcoat Membrane Solids, μg	Topcoat Membrane Thickness, μm	Stent	Drug Loaded in the Drug-Polymer Layer, μg	Amount of the Drug Released in 24 Hours, μg	% of the Drug Released in 24 Hours
1	30	0.54	12 mm VISION	240	139	57.9
2	50	0.89	12 mm VISION	240	58	24.2

TABLE 3-continued

Drug Release Study of Stent Coatings Having PBMA Topcoat Membranes (EVAL-based Drug-Polymer Layer, Etoposide Drug)

No.	Topcoat Membrane Solids, μg	Topcoat Membrane Thickness, μm	Stent	Drug Loaded in the Drug-Polymer Layer, μg	Amount of the Drug Released in 24 Hours, μg	% of the Drug Released in 24 Hours
3	100	1.30	12 mm VISION	240	24	10.0
4	50	0.61	13 mm TETRA	180	148	82.2
5	120	1.46	13 mm TETRA	180	70	38.9
6	200	2.44	13 mm TETRA	180	72	40.0
7	200	2.44	13 mm TETRA	180	41	22.7
8	300	3.86	13 mm TETRA	180	50	27.8

A kinetic study of the drug release profile was conducted. The stent was immersed in a phosphate-buffered saline solution having about 1 mass % of sodium dodecyl sulfate. The solution was frequently sampled and the drug concentration was measured using HPLC. The stent had the total amount of solids of the topcoat membrane of about 30 μg and the total amount of estradiol in the drug-polymer layer of about 160 μg. As seen from the release profile for three different coated stents shown on FIG. **2**, the profile was close to linear and the reproducibility was excellent.

Example 4

A primer layer can be applied onto a stent as described in Example 1. A drug formulation can be prepared comprising:

(a) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of PBMA;

(b) between about 0.1 mass % and about 2 mass %, for example, about 1.6 mass % of a therapeutically active substance, for example, everolimus; and

(c) the balance, a solvent system, for example a 60:40 (mass) blend of acetone and xylene.

The drug containing formulation can then be applied to the stent, and a drug-polymer layer is formed, in a manner identical to that described in Example 1. The solids contents of the drug-polymer layer can be 1,200 μg.

Finally, a topcoat composition to control the drug release rate can be prepared, comprising between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % PBMA and the balance a solvent system, for example, a solvent system including a 10:50:40 (mass) blend of acetone, Techspray's FLUX REMOVER AMS and xylene, and the topcoat membrane can be formed, in a manner identical to that described in Example 1. The topcoat membrane can have a solids content of between about 20 μg and about 200 μg, for example, about 30 μg.

Example 5

A primer layer can be applied onto a 8-mm stent as described in Example 1. A drug formulation can be prepared comprising:

(a) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of PBMA;

(b) between about 0.1 mass % and about 2 mass %, for example, about 1.6 mass % of a therapeutically active substance, for example, Everolimus; and

(c) the balance, a solvent system, for example a 60:40 (mass) blend of acetone and xylene.

The drug formulation can then be applied onto the stent, and a drug-polymer layer is formed in a manner identical to that described in Example 1. The solids contents of the drug-polymer layer can be 1,200 μg. In this Example, the stent coating has no separate topcoat membrane.

Example 6

A primer layer can be applied onto a 8-mm stent as described in Example 1. A drug formulation can be prepared comprising:

(a) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of P(MMA-BMA) having a weight-average molecular weight M_w of about 150,000 available from Aldrich Chemical Company under the name PBM 150;

(b) between about 0.1 mass % and about 2 mass %, for example, about 1.0 mass % of an active agent, for example, Everolimus; and

(c) the balance, a solvent system, for example a 10:50:40 (mass) blend of acetone, Techspray's FLUX REMOVER AMS and xylene.

PBM 150 contains about 79.2 mass % of units derived from BMA. The drug formulation can then be applied onto the dried primer layer, and a drug-polymer layer is formed, in a manner identical to that described in Example 1. The drug-polymer layer can have the total amount of solids of between about 300 and 600 μg, for example, about 520 μg. In this Example, the stent coating has no separate topcoat membrane.

Example 7

A primer layer and a drug-polymer layer can be applied onto a stent as described in Example 1, the drug-polymer layer having the total amount of EVAL between about 300 and 800 μg, for example, about 325 μg. A topcoat composition to control the drug release rate can be prepared, comprising between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % P(MMA-BMA) having about 66.5 mass % of units derived from BMA, and the balance of a solvent system, for example, a solvent system including a 10:50:40 (mass) blend of acetone, Techspray's FLUX REMOVER AMS and xylene. The topcoat membrane can be

formed having the total amount of solids between about 20 and 200 μg, for example, about 30 μg.

Example 8

A primer layer and a drug-polymer layer can be applied onto a stent as described in Example 1, the drug-polymer layer having the total amount of EVAL between about 300 and 800 μg, for example, about 380 μg. A topcoat composition to control the drug release rate can be prepared, comprising between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of a 1:1 (by mass) blend of P(MMA-BMA) and PBMA, and the balance of a solvent system, for example, the solvent system including a 10:50:40 (mass) blend of acetone, Techspray's FLUX REMOVER AMS and xylene. The P(MMA-BMA)/PBMA blend can have about 83.3 mass % of units derived from BMA. The topcoat membrane can be formed having the total amount of solids between about 20 and 200 μg, for example, about 30 μg.

Example 9

A primer layer and a drug-polymer layer can be applied onto a stent as described in Example 1, the drug-polymer layer having the total amount of EVAL between about 300 and 800 μg, for example, about 350 μg. A topcoat composition to control the drug release rate can be prepared, comprising between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of a 2:1 (by mass) blend of P(MMA-BMA) and PBMA, and the balance a solvent system, for example, a solvent system including a 10:50:40 (mass) blend of acetone, Techspray's FLUX REMOVER AMS and xylene. The P(MMA-BMA)/PBMA blend can have about 77.8 mass % of units derived from BMA. The topcoat membrane can have a total amount of solids between about 20 and 200 μg, for example, about 28 μg.

Example 10

A primer layer and a drug-polymer layer can be applied onto a stent as described in Example 9. A topcoat composition to control the drug release rate can be prepared, comprising between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of a 4:1 (by mass) blend of P(MMA-BMA) and PBMA, and the balance a solvent system, for example, a solvent system including a 10:50:40 (mass) blend of acetone, Techspray's FLUX REMOVER AMS and xylene. The P(MMA-BMA)/PBMA blend can have about 73.3 mass % of units derived from BMA. The topcoat membrane can have a total amount of solids between about 20 and 200 μg, for example, about 32 μg.

Example 11

A primer layer and a drug-polymer layer can be applied onto a stent as described in Example 9. A topcoat composition to control the drug release rate can be prepared, comprising between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of PEMA, and the balance a solvent system, for example, a solvent system including a 80:20 (mass) blend of acetone and cyclohexanone. Poly (ethyl methacrylate) having a weight-average molecular weight M_w of about 101,400 available from Aldrich Chemical Company is one example of a brand of PEMA that can be used. In a manner identical to the application of the primer layer and the drug-polymer layer, the topcoat composition can be applied onto the dried drug-polymer layer. A number of spray passes can be performed followed by final baking, first at about 60° C. for about 2 hours and then at about 140° C. for about 1 hour. The topcoat membrane can be formed, the membrane having a solids content of between about 20 μg and about 300 μg, for example, about 40 μg.

Example 12

A primer layer and a drug-polymer layer can be applied onto a stent as described in Example 9. A topcoat composition to control the drug release rate can be prepared, comprising between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of a blend of PEMA with a fluorinated polymer; and the balance a solvent system, for example, a solvent system including a 50:50 (mass) blend of acetone and cyclohexanone. The brand of PEMA described in Example 10 can be used. One example of the fluorinated polymer that can be used in a blend with PEMA is PVDF-HFP, such as SOLEF 21508 having about 85 mass % of vinylidene fluoride-derived units and about 15 mass % of hexafluoro propene-derived units. SOLEF 21508 is available from Solvay Fluoropolymers, Inc. of Houston, Tex. The PEMA/SOLEF 21508 blend can be 3:1 (mass) (containing about 75 mass % of PEMA and about 25 mass % of SOLEF 21508). In a manner identical to the application of the primer layer and the drug-polymer layer, the topcoat composition can be applied onto the dried drug-polymer layer. A number of spray passes can be performed followed by final baking, first at about 60° C. for about 2 hours and then at about 100° C. for about 1 hour. The topcoat membrane can have a solids content of between about 20 μg and about 300 μg, for example, about 42 μg.

Example 13

A stent was coated as described in Example 12, except instead of the 3:1 PEMA/SOLEF 21508 blend, a 3:1 (mass) blend of PEMA/PBMA can be used to form the topcoat membrane. The dry topcoat membrane can have a solids content of between about 20 μg and about 300 μg, for example, about 50 μg.

Example 14

A stent was coated as described in Example 13, except instead of the 3:1 PEMA/PBMA blend, a 1:1 (mass) blend of PEMA/PBMA can be used to form the topcoat membrane (containing about 50 mass % of PEMA and about 50 mass % of PBMA).

Example 15

A primer layer and a drug-polymer layer can be applied onto a stent as described in Example 4. A topcoat composition to control the drug release rate can be prepared, comprising between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of a 1:1 (by mass) blend of PBMA and EVAL, and the balance a solvent system, for example, a solvent system including a 80:20 (mass) blend of DMAC and pentane. The topcoat membrane can have a total amount of solids of between about 20 and 200 μg, for example, about 30 μg.

Example 16

A primer layer can be applied onto a stent as described in Example 1. A drug formulation can be prepared comprising:

(a) between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % of a 1:1 (by mass) blend of PBMA and EVAL;

(b) between about 0.1 mass % and about 2 mass %, for example, about 1.6 mass % of a therapeutically active substance, for example, Everolimus; and

(c) the balance, a solvent system, for example, a solvent system which includes a 80:20 (mass) blend of DMAC and pentane.

The drug containing formulation can then be applied onto the stent. The solids contents of the drug-polymer layer can be 1,200 μg.

Example 17

A primer layer and a drug-polymer layer can be applied onto a stent as described in Example 16. A topcoat composition to control the drug release rate can be prepared, comprising between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % PBMA and the balance a solvent system, for example, a solvent system including a 10:50:40 (mass) blend of acetone, Techspray's FLUX REMOVER AMS and xylene. The topcoat membrane can have a solids content of between about 20 μg and about 200 μg, for example, about 30 μg.

Example 18

A primer layer and a drug-polymer layer can be applied onto a stent as described in Example 16. A topcoat composition to control the drug release rate can be prepared as described in Example 15. The topcoat membrane can have a total amount of solids between about 20 and 200 μg, for example, about 30 μg.

Example 19

A primer layer and a drug-polymer layer can be applied onto a stent as described in Example 1. A topcoat composition to control the drug release rate can be prepared as described in Example 15. The topcoat membrane can be formed, in a manner identical to that described in Example 1, the topcoat membrane having the total amount of solids between about 20 and 200 μg, for example, about 30 μg.

Example 20

A primer layer and a drug-polymer layer can be applied onto a stent as described in Example 16. A topcoat composition to control the drug release rate can be prepared, the composition comprising between about 0.1 mass % and about 15 mass %, for example, about 2.0 mass % EVAL and the balance DMAC solvent The topcoat membrane can be formed, in a manner identical to that described in Example 1.

The information discussed in Examples 1-20 is summarized in Table 4.

TABLE 4

Summary of Examples 1–20

Example No.	Polymer of the Drug-Polymer Layer	Drug	Polymer of the Topcoat Matrix
1	EVAL	Everolimus	PBMA
2	EVAL	Estradiol	PBMA
3	EVAL	Etoposite	PBMA
4	PBMA	Everolimus	PBMA
5	PBMA	Everolimus	None
6	P(MMA-BMA)	Everolimus	None
7	EVAL	Everolimus	P(MMA-BMA)
8	EVAL	Everolimus	1:1 blend of P(MMA-BMA) and PBMA
9	EVAL	Everolimus	2:1 blend of P(MMA-BMA) and PBMA
10	EVAL	Everolimus	4:1 blend of P(MMA-BMA) and PBMA
11	EVAL	Everolimus	PEMA
12	EVAL	Everolimus	3:1 blend of PEMA and P(VDF-HFP)
13	EVAL	Everolimus	3:1 blend of PEMA and PBMA
14	EVAL	Everolimus	1:1 blend of PEMA and PBMA
15	PBMA	Everolimus	1:1 blend of PBMA and EVAL
16	1:1 blend of PBMA and EVAL	Everolimus	None
17	1:1 blend of PBMA and EVAL	Everolimus	PBMA
18	1:1 blend of PBMA and EVAL	Everolimus	1:1 blend of PBMA and EVAL
19	EVAL	Everolimus	1:1 blend of PBMA and EVAL
20	1:1 blend of PBMA and EVAL	Everolimus	EVAL

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

What is claimed is:

1. A coating for an implantable medical device, comprising

a layer comprising:

a copolymer comprising butyl methacrylate and one or two other alkyl acrylates or

alkyl methacrylates; or,

the aforementioned copolymer blended with one or more other non-acrylate polymers or copolymers; and,

a therapeutically active agent, wherein:

the alkyl of the one or two other acrylates or methacrylates is a C_1 to C_{12} straight chained or branched aliphatic radical; and,

the layer is free of acetate species.

2. The coating of claim **1**, wherein the implantable medical device is a stent.

3. The coating of claim **1**, wherein the therapeutically active agent is rapamycin a derivative thereof or an analog thereof.

4. The coating of claim **1**, wherein the butyl methacrylate copolymer comprises an n-butyl methacrylate copolymer.

5. The coating of claim **1**, wherein the non-acrylate polymers or copolymers are fluorinated polymers or copolymers.

6. The coating of claim **5**, wherein the fluorinated polymer or copolymer is selected from the group consisting of poly(vinylidene fluoride) and poly(vinylidene fluoride-co-hexafluoropropene).

7. A coating for an implantable medical device, the coating comprising a first layer having an active agent incorporated therein and a second layer disposed over the first layer, wherein the second layer comprises:

a copolymer comprising butyl methacrylate and one or two other alkyl acrylates or alkyl methacrylates; or,

the aforementioned copolymer blended with one or more other non-acrylate polymers or copolymers; wherein:

the alkyl of the one or two other acrylates or methacrylates is a C_1 to C_{12} straight chained or branched aliphatic radical; and,

the second layer is free from acetate species.

8. The coating of claim **7**, wherein the implantable medical device is a stent.

9. The coating of claim **7**, wherein the agent is for reducing, inhibiting or lowering the incidence of restenosis.

10. The coating of claim **7**, wherein the butyl methacrylate copolymer comprises poly(n-butyl methacrylate).

11. The coating of claim **7**, wherein the non-acrylate polymers or copolymers are fluorinated polymers or copolymers.

12. The coating of claim **11**, wherein the fluorinated polymer or copolymer is selected from the group consisting of poly(vinylidene fluoride) and poly(vinylidene fluoride-co-hexafluoropropene).

13. A method of coating an implantable medical device, comprising depositing a first layer on the device, the first layer including an active agent for the sustained release of the agent, and depositing a second layer over the first layer, the second layer comprising:

a copolymer comprising butyl methacrylate and one or two other alkyl acrylates or alkyl methacrylates; or,

the aforementioned copolymer blended with one or more other non-acrylate polymers or copolymers; wherein:

the alkyl of the one or two other acrylates or methacrylates is a C_1 to C_{12} straight chained or branched aliphatic radical; and,

the second layer is free of acetate species.

14. The method of claim **13**, wherein the implantable medical device is a stent.

15. The method of claim **13**, wherein the therapeutically active agent is rapamycin, a derivative thereof or an analog thereof.

16. The method of claim **13**, wherein the butyl methacrylate copolymer comprises an n-butyl methacrylate copolymer.

17. The coating of claim **1**, wherein the non-acrylate polymer is poly(ethylene-co-vinyl alcohol).

18. The coating of claim **7**, wherein the non-acrylate polymer is poly(ethylene-co-vinyl alcohol).

19. The coating of claim **13**, wherein the non-acrylate polymer is poly(ethylene-co-vinyl alcohol).

20. The coating of claim **1**, wherein the therapeutically active agent is a 40-O-derivative of rapamycin.

21. The method of claim **13**, wherein the therapeutically active agent is a 40-O-derivative of rapamycin.

* * * * *

US007279174B2

(12) **United States Patent**
Pacetti et al.

(10) **Patent No.: US 7,279,174 B2**
(45) **Date of Patent: Oct. 9, 2007**

(54) **STENT COATINGS COMPRISING HYDROPHILIC ADDITIVES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 725 days.

(21) Appl. No.: **10/431,711**

(22) Filed: **May 8, 2003**

(65) **Prior Publication Data**

US 2004/0224001 A1 Nov. 11, 2004

(51) **Int. Cl.**
A61F 13/00 (2006.01)

(52) **U.S. Cl.** **424/422**

(58) **Field of Classification Search** 424/422; 623/1.42

See application file for complete search history.

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(57) **ABSTRACT**

A coating for implantable medical devices and a method for fabricating thereof are disclosed. The coating includes a mixture of a hydrophobic polymer and a polymeric hydrophilic additive, wherein the hydrophobic polymer and the hydrophilic additive form a physically entangled or interpenetrating system.

22 Claims, 2 Drawing Sheets

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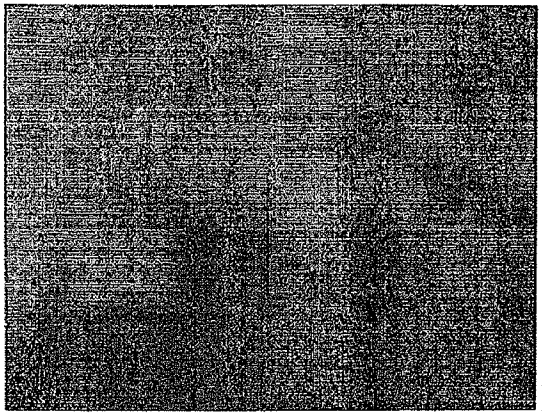

FIG. 1

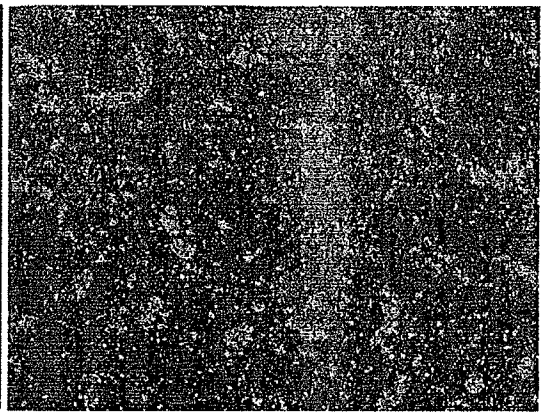

FIG.2

FIG. 3

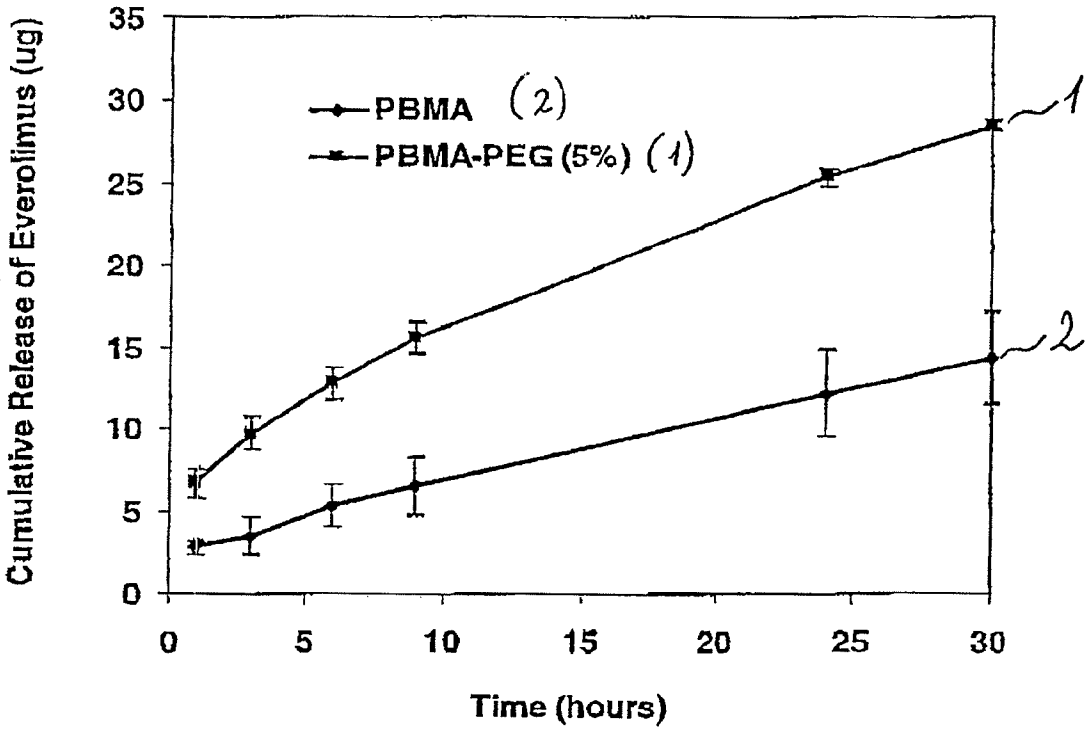
Cumulative Release of Everolimus (ug)
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
Time (hours)
PBMA (2)
PBMA-PEG (5%) (1)
1
2

FIG. 4

STENT COATINGS COMPRISING HYDROPHILIC ADDITIVES

BACKGROUND

1. Field of the Invention

This invention relates to implantable medical devices such as stents. More particularly, the invention relates to materials that can be used to coat stents.

2. Description of Related Art

In the field of medical technology, there is frequently a necessity to administer drugs locally. To provide an efficacious concentration to the treatment site, systemic administration of medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. For the treatment of vascular lesions, stents can be modified with a polymeric coating to provide local drug delivery capabilities.

Examples of polymers that can be used to coat stents or other implantable devices include hydrophobic polymers, for example, poly(meth)acrylates, such as poly(n-butyl methacrylate) (PBMA) and copolymers or terpolymers having units derived from n-butyl methacrylate (BMA). PBMA and BMA-based coatings can provide effective control of the rate of release of a drug from a stent. In addition, PBMA and BMA-based polymers are biocompatible, have good adhesion to the underlying stent surface, are easily processable, and possess good physical and mechanical properties such as ability to withstand elongation, compression, and shear that the stent undergoes during crimping onto the catheter, delivery to the lesion site, and expansion.

The properties of PBMA and BMA-based stent coatings can be improved, however. For example, permeability of such coatings can be too low, particularly for drugs having higher molecular weights, leading to potentially insufficient supply of the drug to the diseased site. An ability to better regulate the rate of release through the coatings is desired. The present invention provides such coatings.

BRIEF DESCRIPTION OF DRAWINGS

FIGS. **1-3** are optical micrographs of coatings according to various embodiments of the present invention.

FIG. **4** is a graph illustrating kinetics of in vitro release of a drug through one stent coating of the present invention.

SUMMARY

An implantable medical device comprising a coating is provided, the coating includes a mixture of at least one poly(meth)acrylate and at least one polyalkylene glycol, wherein the macromolecular chains of the poly(meth)acrylate and the polyalkylene glycol form a physically entangled or interpenetrating system. Examples of the poly(meth) acrylate include poly(methyl methacrylate), poly(ethyl methacrylate), poly(n-propyl methacrylate), poly(iso-propyl methacrylate), poly(n-butyl methacrylate), poly(iso-butyl methacrylate), poly(tert-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(n-propyl acrylate), poly (iso-propyl acrylate), poly(n-butyl acrylate), poly(iso-butyl acrylate), and mixtures thereof. Examples of the polyalkylene glycol include poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol), poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.

An implantable medical device comprising a coating is provided, the coating includes a mixture of at least one hydrophobic polymer and at least one polymeric hydrophilic compound, wherein the macromolecular chains of the hydrophobic polymer and the hydrophilic compound form a physically entangled or interpenetrating system. The hydrophobic polymer can include poly(meth)acrylates, vinyl polymers, polyolefins, halogenanated polymers, polymers having urethane groups, polybutyrals, nylon, silicones, polycarbonate, or polysulfone. The polymeric hydrophilic compound can include polyalkylene glycols, hyaluronic acid, chondroitan sulfate, chitosan, glucosaminoglucans, dextran, dextrin, dextran sulfate, cellulose acetate, carboxymethyl cellulose, hydroxyethyl cellulose, cellulosics, polypeptides, poly(2-hydroxyethyl methacrylate), polyacrylamide, polyacrylimide, poly(ethylene amine), poly(allyl amine), poly(vinyl pyrrolidone), poly(vinyl alcohol), poly (acrylic acid), poly(methacrylic acid), acrylic acid copolymers, methacrylic acid copolymers, polyvinyl alkyl ethers, non-ionic tetrafunctional block-copolymer surfactants, gelatin, collagen, albumin, chitin, heparin, elastin, fibrin, and mixtures thereof.

A medical article comprising an implantable substrate and a coating is provided, the coating includes a bulk polymer, an additive polymer in less quantity in the coating that the bulk polymer, the additive polymer being entangled or interpenetrated with the bulk polymer, and a drug.

A method for fabricating a coating for an implantable medical device is provided, the method comprises forming a coating on the device, the coating including a mixture of at least one hydrophobic polymer and at least one polymeric hydrophilic compound, wherein the macromolecular chains of the hydrophobic polymer and the hydrophilic compound form a physically entangled or intertwined system.

DETAILED DESCRIPTION

A coating for an implantable medical device, such as a stent, can include an optional primer layer, a drug-polymer layer, and an optional topcoat layer. The drug-polymer layer can be applied directly onto at least a part of the stent surface to serve as a reservoir for an active agent or a drug which is incorporated into the drug-polymer layer. An optional primer layer can be applied between the stent and the drug-polymer layer to improve the adhesion of the drug-polymer layer to the stent. An optional topcoat layer can be applied over at least a part of the drug-polymer layer to reduce the rate of release of the drug from the reservoir.

The topcoat layer, if used, is the outermost layer of the stent coating. If the topcoat layer is not used, the drug-polymer layer is the outermost layer of the stent coating. The drug-polymer and/or topcoat layer of the stent coating can include at least one hydrophobic polymer. To regulate a rate of release of the drug from the drug-polymer layer the hydrophobic polymer(s) can be physically mixed or blended with at least one polymeric hydrophilic additive to form a polymer system where the macromolecular chains of the hydrophobic polymer and the hydrophobic additive are physically entangled, miscible, and/or interpenetrating. This polymer system can be, in one embodiment, the outermost region or layer of the coating.

Hereinafter, the hydrophobic polymer is also referred to as "polymer," and polymeric hydrophilic additive is also referred to as "additive." The term "physically entangled" is defined hereinafter as a polymer/additive composition in which neither the polymer nor the additive forms a separate phase domain having a size larger than about 100 nanom-

eters, such as the size larger than about 200 nanometers, for example, larger than about 300 nanometers. The size of the domain is determined by the largest linear dimension of the domain particle, e.g., by the diameter of a particle in case the domain particles are spheres. The definition of "physically entangled" also includes a condition that once the polymer and the additive have become physically entangled, they do not disentangle but remain physically entangled for the duration of the service of the coating or until the drug has been released from the coating.

The hydrophobic polymer and the hydrophobic additive are defined hereinafter as "miscible" if the thermogram of the polymer/additive mixture shows substantially no thermal transitions attributable to either the essentially pure polymer or the essentially pure additive. The thermogram can be obtained by a standard method of thermal analysis known to those having ordinary skill in the art, for example, by the method of differential scanning calorimetry.

The term "interpenetrating" is defined as the polymer/additive system where the polymer and the additive form an interpenetrating polymer network (IPN). The definition of the IPN used by the International Union of Pure and Applied Chemistry (IUPAC) is adopted herein. The IUPAC describes the IPN as a polymer comprising two or more networks which are at least partially interlaced on a molecular scale, to form both chemical and physical bonds between the networks. The networks of an IPN cannot be separated unless chemical bonds are broken. In other words, an IPN structure represents two or more polymer networks that are partially chemically cross-linked and partially physically entangled.

To define the terms "hydrophobic" and "hydrophilic" for the purposes of the present invention, one of the two criteria can be used. According to one criterion, a component in the polymer/additive system (i.e., the polymer or the additive) can be classified by the value of the component's equilibrium water adsorption. Whichever component in the polymer/additive system has the greater value of the equilibrium water adsorption at room temperature is considered hydrophilic and the other component is considered hydrophobic. If more than two components are used in the polymer/additive system, then each can be ranked in order of its equilibrium water adsorption value. In one embodiment, the polymer is considered hydrophobic if it has an equilibrium water adsorption less than 10 mass % at room temperature, and the additive is considered hydrophilic if it has an equilibrium water adsorption at room temperature of 10 mass % or greater.

According to another criterion, a component in the polymer/additive system can be classified by the value of the component's Hildebrand solubility parameter δ. The term "Hildebrand solubility parameter" refers to a parameter measuring the cohesion of a substance and is determined as follows:

$$\delta=(\Delta E/V)^{1/2}$$

where δ is the solubility parameter, $(cal/cm^3)^{1/2}$;

ΔE is the energy of vaporization, cal/mole; and

V is the molar volume, cm^3/mole.

Whichever component in the polymer/additive system has lower δ value compared to the δ value of the other component in the blend is designated as a hydrophobic component, and the other component with higher δ value is designated as hydrophilic. If more than two components are used in the blend, then each can be ranked in order of its δ value. In one exemplary embodiment, the δ value defining the boundary between the hydrophobic and hydrophilic components of the polymer/additive system can be about 10.7 $(cal/cm^3)^{1/2}$.

Hydrophobic substances typically have a low δ value. In one embodiment, a component in the polymer/additive system that is "hydrophobic" can have a Hildebrand solubility parameter lower than about 10.7 $(cal/cm^3)^{1/2}$. A component in the polymer/additive system that is "hydrophilic" can have a solubility parameter greater than about 10.7 $(cal/cm^3)^{1/2}$.

To make the polymer/additive mixture, the polymer can be blended with the additive and the blend can be dissolved in a solvent or in a system comprising a mixture of solvents. The term "dissolved" means that the polymer/additive blend, when combined with a suitable solvent or a mixture of solvents, is capable of forming a system which can be applied on a stent by a common technique, such as spraying or dipping. The solvent or a mixture of solvents can be selected by those having ordinary skill in the art depending, among other factors, on the nature of the polymer and the additive.

The polymer/additive solution can be then applied on the stent by a commonly known technique known to those having ordinary skill in the art, for example, by spraying or dipping, followed by drying, for example, by baking. The polymer/additive solution can be used to form the topcoat layer and/or the drug-polymer layer of the stent coating.

The combined mass concentration of the polymer and the additive in the polymer/additive solution can be between about 1% and about 10%, for example, about 2%. A ratio between the hydrophobic polymer and the polymeric hydrophilic additive in the polymer/additive solution can be between about 99:1 and about 9:1, such as between about 74:1 and about 14:1, more narrowly between about 49:1 and about 19:1. For example, for a polymer/additive solution containing about 2 mass % of the hydrophobic polymer, the concentration of the polymeric hydrophilic additive can be between about 0.04 and about 0.1 mass % of the total mass of the solution.

The polymer/additive solution can be prepared by various alternative methods. For example, the hydrophobic polymer and the polymeric hydrophilic additive can be dissolved separately to obtain a hydrophobic polymer solution and a polymeric hydrophilic additive solution, followed by combining the two solutions to form the polymer/additive solution. Alternatively, the hydrophobic polymer can be dissolved first to form the hydrophobic polymer solution, followed by adding the polymeric hydrophilic additive to the hydrophobic polymer solution to form the polymer/additive solution. As another alternative, the additive can be dissolved first to form the additive solution followed by adding the polymer to form the polymer/additive solution.

Examples of hydrophobic polymers include poly(meth) acrylates. The term "poly(meth)acrylates" refers to both polymethacrylates and polyacrylates. Examples of poly (meth)acrylates that can be used include homo-and copolymers of butyl methacrylate, for example PBMA, poly(vinylidene fluoride-co butyl methacrylate), or poly(methyl methacrylate-co-butyl methacrylate). Representative examples of other hydrophobic polymers that can be used in practice of the present invention include the following polymers and mixtures thereof:

(a) poly(meth)acrylates other than PBMA or BMA-based polymethacrylates, such as poly(methyl methacrylate), poly(ethyl methacrylate), poly(n-propyl methacrylate), poly(iso-propyl methacrylate), poly(iso-butyl methacrylate), poly(tert-butyl methacrylate), poly(methyl

acrylate), poly(ethyl acrylate), poly(n-propyl acrylate), poly(iso-propyl acrylate), poly(n-butyl acrylate), and poly(iso-butyl acrylate);

(b) vinyl polymers such as poly(ethylene-co-vinyl alcohol), for example, poly(ethylene-co-vinyl alcohol) having a molar content of ethylene-derived units of at least 44%, poly(ethylene-co-vinyl acetate), poly(vinyl acetate), polystyrene, poly(styrene-co-iso-butylene), poly(styrene-co-ethylene-co-butylene-co-styrene) terpolymers, and poly(styrene-co-butadiene-co-styrene) terpolymers;

(c) polyolefins, for example, atactic polypropylene;

(d) halogenanated (e.g., fluorinated or chlorinated) polymers such as poly(vinyl fluoride), poly(vinylidene fluoride), polyhexafluoropropene, poly(hexafluoropropene-co-vinylidene fluoride), poly(ethylene-co-hexafluoropropene), various grades of amorphous TEFLON (including polytetrafluoroethylene) available from E.I. Du Pont de Nemours & Co., poly(vinyl chloride), and poly(vinylidene chloride);

(e) polymers having urethane groups, such as polyether urethanes, polyester urethanes, polyurethaneureas, polycarbonate urethanes, and silicone urethanes; and

(f) polybutyrals, nylon, silicones, polycarbonate, and polysulfone.

Representative examples of polymeric hydrophilic additives that can be used in practice of the present invention include hyaluronic acid, chondroitan sulfate, chitosan, glucosaminoglucans, dextran, dextrin, dextran sulfate, cellulose acetate, carboxymethyl cellulose, hydroxyethyl cellulose, cellulosics, poly(ethylene glycol)(PEG), poly(ethylene oxide), poly(propylene glycol), PLURONIC, TETRONIC, poly(trimethylene glycol), poly(tetramethylene glycol), polypeptides, poly(2-hydroxyethyl methacrylate), polyacrylamide, polyacrylimide, poly(ethylene amine), poly(allyl amine), poly(vinyl pyrrolidone), poly(vinyl alcohol), poly (acrylic acid), poly(methacrylic acid), acrylic acid copolymers, methacrylic acid copolymers, polyvinyl alkyl ethers such as poly(vinylmethyl ether) or poly(vinylethyl ether); gelatin, collagen, albumin, chitin, heparin, elastin, fibrin and mixtures thereof. PLURONIC is a trade name of a poly (ethylene oxide-co-propylene oxide). TETRONIC is a trade name of a family of non-ionic tetrafunctional block-copolymer surfactants. PLURONIC and TETRONIC are available from BASF Corp. of Parsippany, N.J.

To achieve the physical entanglement of the hydrophobic polymer and polymeric hydrophilic additive, at least one polymer and at least one additive can be blended together in a common solvent system that includes at least one very volatile solvent, followed by applying the solution onto a stent, for example, by spraying. As used herein, "very volatile solvent" means a solvent that has a vapor pressure greater than 30 Torr at ambient temperature. Examples of very volatile solvent include acetone and methyl ethyl ketone. Alternatively, to physically entangle the hydrophobic polymer and polymeric hydrophilic additive, the polymer and the additive can be blended in the melt, and then applied to the stent from the melt, for example by curtain coating.

One way of forming an interpenetrating system of the hydrophobic polymer and polymeric hydrophilic additive is by blending the polymer and the additive in a solvent, or solvent blend, in which both components are soluble. The solution can be applied onto a stent, for example, by spraying, followed by the removal of the solvent by drying. For the polymer and the additive which are capable of forming an interpenetrating system, the polymers and the additive are expected to interpenetrate while still in solution, and to remain interpenetrated upon solvent removal.

Alternatively, to form an interpenetrating system of the hydrophobic polymer and polymeric hydrophilic additive, the polymer and additive, which can be polymerized according to two different mechanisms, can be selected. For example, the hydrophobic component can be a carbonate urethane that is polymerized by condensation reactions between isocyanate and hydroxyl groups, while the hydrophilic additive can be poly(2-hydroxyethyl methacrylate) that polymerizes by a free radical mechanism. The monomers may be dissolved in a common solvent system, applied to the stent, and then polymerized directly on the stent.

As another alternative way of forming an interpenetrating system of the hydrophobic polymer and polymeric hydrophilic additive, a high molecular weight polymer and additive can be selected, each component having reactive or associative groups that can interact with the reactive or associative groups of the other component. For example, such hydrophilic additive as hydroxy terminated PEG can be blended with a high molecular weight, hydrophobic polyurethane with active isocyanate groups along the backbone. The additive and the polymer can be blended in solution, sprayed onto a stent, followed by curing. Although sometimes the two components may be not miscible, the covalent bonds between them can still prevent phase separation.

To facilitate the formation of an entangled and/or interpenetrating hydrophobic polymer-polymeric hydrophilic additive system, the polymer and the additive can be selected in such a way that the chain lengths of the polymer and the additive, as determined by degree of polymerization, are such as to promote the entanglement and/or interpenetration of the macromolecules of the polymer and the additive. The term "degree of polymerization" refers to a number of repeating monomeric units in a single macromolecule. The chain lengths that promote the formation of an entangled and/or interpenetrating network can be such that the contour length of the hydrophilic additive lies in the range of between about 10% and about 100% of the contour length of the hydrophobic polymer, for example, between 50% and 100%, such as 80%. The term "contour length" refers to the combined length of all bonds along the main chain (the backbone) of a macromolecule. The contour length can be approximated as the degree of polymerization multiplied by the number of bonds in the repeat unit. An average bond length of about 1.4 Å can be used for the computation. The following example can be used to illustrate how the molecular weights of the polymer and the additive can be chosen to achieve a proper ratio between the contour lengths of the polymer and the additive.

PBMA with a number-averaged molecular weight (M_n) of about 200,000, has a degree of polymerization of 1,408 and has 2 bonds in the polymer backbone per repeat unit. Thus, a contour length of a PBMA macromolecule is about 3,940 Å. Suitable hydrophilic additive to achieve entanglement can be PEG having contour lengths between about 394 Å and about 3,940 Å. PEG has 3 bonds per repeat unit, so for PEG having contour lengths between about 394 Å and about 3,940 Å, corresponding degree of polymerization is approximately between 131 and 1,313, and the corresponding M_n is between about 5,780 and about 57,800.

Generally, M_n of the hydrophobic polymer can be between about 50,000 and 1000,000 Daltons, for example, about 100,000 Daltons. The molecular weight of the hydrophilic additive can be between about 5,000 and about 100,000 Daltons, for example, about 40,000 Daltons. If PBMA is used as the hydrophobic polymer, the molecular

weight of PBMA can be between about 100,000 and about 300,000 Daltons, for example, about 200,000 Daltons. If PEG is used as the hydrophilic additive being mixed with PBMA, the molecular weight of PEG can be between about 10,000 and about 60,000 Daltons, for example, about 20,000 Daltons.

The embodiments of the present invention are described in connection with a stent, e.g., balloon expandable or self-expandable stents; however, other implantable medical devices can also be coated. Examples of such implantable devices include stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corp. of Santa Clara, Calif.). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co. of Jenkintown, Pa. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention. The device itself can be made in whole or in part from the disclosed polymeric blends.

For the drug-polymer layer, the coating can include an active agent or a drug. The drug can include any substance capable of exerting a therapeutic or prophylactic effect for a patient. The drug may include small molecule drugs, peptides, proteins, oligonucleotides, and the like. The drug could be designed, for example, to inhibit the activity of vascular smooth muscle cells. It can be directed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells to inhibit restenosis.

Examples of drugs include antiproliferative substances such as actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich of Milwaukee, Wis., or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g. TAXOL® by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g. Taxotere®, from Aventis S.A., Frankfurt, Germany), methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin® from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin® from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as Angiomax™ (Biogen, Inc., Cambridge, Mass.). Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten® and Capozide® from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil® and Prinzide® from Merck & Co., Inc., Whitehouse Station, N.J.); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor® from Merck & Co., Inc., Whitehouse Station, N.J.), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and donors of nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, tacrolimus, dexamethasone, and rapamycin and structural derivatives or functional analogs thereof, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of EVEROLIMUS available from Novartis), 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-O-tetrazole-rapamycin.

The molecular weight of the drug can influence the choice of the molecular weights of the polymer and the additive, as well as the ratios between the polymer and the additive, since the release rate of the drugs having higher molecular weights is expected to be slower compared with the release rate of the drugs with lower molecular weights. To illustrate, when the PBMA/PEG topcoat system is used in conjunction with EVEROLIMUS (having molecular weight 958 Daltons), M, of PBMA can be between about 90,000 Daltons and about 300,000 Daltons, for example, about 190,000 Daltons and M_n of PEG can be between about 6,000 Daltons and about 20,000 Daltons, for example, about 18,000 Daltons, and the mass ratio between PBMA and PEG can be between about 49:1 and about 9:1, for example, about 20:1. At the same time, in the case of estradiol (having molecular weight of 272), M_n of PBMA can be between about 150,000 Daltons and about 900,000 Daltons, for example, about 300,000 Daltons and M_n of PEG can be between about 10,000 Daltons and about 50,000 Daltons, for example, about 30,000 Daltons, and the mass ratio between PBMA and PEG can be between about 99:1 and about 25:1, for example about 49:1.

Embodiments of the present invention are further illustrated by the following examples.

EXAMPLE 1

A first polymer solution was prepared, the solution containing:

(a) about 5 mass % of poly(n-butyl methacrylate) (PBMA) having M_n of about 154,000; and

(b) the balance, solvent mixture of acetone and cyclohexanone, the mixture having a mass ratio between acetone and cyclohexanone of about 4:1.

A second polymer solution was prepared, the solution containing:

(a) about 5 mass % of poly(ethylene glycol) (PEG) having M_n of about 18,000; and

(b) the balance, solvent mixture of acetone and cyclohexanone, the mixture having a mass ratio between acetone and cyclohexanone of about 4:1.

The first polymer solution was combined with the second polymer solution to prepare a PBMA/PEG solution. The amount of the first and second polymer solutions were

selected to obtain the PBMA/PEG solution having a mass ratio between PBMA and PEG of about 49:1.

The PBMA/PEG solution was cast on a glass slide, and the solvent was removed by drying at room temperature followed by baking at about 80° C. for about 1 hour. As a result, an adhered polymer film was formed on the glass slide. An optical micrograph of the dry PBMA/PEG film was taken in transmitted polarized light, as shown by FIG. **1**. Under such light, amorphous polymers appear dark and crystalline polymers appear bright. As seen from FIG. **1**, the PBMA/PEG system appears uniformly dark showing good miscibility of PBMA and PEG. FIG. **1** does not show that PEG forms a separate phase.

EXAMPLE 2

A PBMA/PEG solution was prepared as described in Example 1, except the mass ratio between PBMA and PEG in the PBMA/PEG solution was about 19:1. A polymer film was formed on a glass slide out of the PBMA/PEG solution as described in Example 1. An optical micrograph of the dry PBMA/PEG film was taken as described in Example 1. The micrograph is shown by FIG. **2**. As seen from FIG. **2**, the PBMA/PEG system appears mostly uniform, with some amount of the crystalline phase formed by PEG represented by bright spots on the micrograph.

EXAMPLE 3

A PBMA/PEG solution was prepared as described in Example 1, except the mass ratio between PBMA and PEG in the PBMA/PEG solution was about 10:1. A polymer film was formed on a glass slide out of the PBMA/PEG solution as described in Example 1. An optical micrograph of the dry PBMA/PEG film was taken as described in Example 1. The micrograph is shown by FIG. **3**. As seen from FIG. **3**, the PBMA/PEG system includes visible crystalline areas. Compared with the film described in Example 2, the film shown by FIG. **3** included more substantial amount of the crystalline phase formed by PEG.

EXAMPLE 4

A first composition was prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass % of poly(ethylene-co-vinyl alcohol) (EVAL); and

(b) the balance, DMAC solvent.

The first composition was applied onto the surface of a bare 18 mm VISION stent (available from Guidant Corp.) by spraying and dried to form a primer layer. A spray coater was used, having a 0.014 fan nozzle maintained at about 60° C. with a feed pressure of about 0.2 atm (about 3 psi) and an atomization pressure of about 1.3 atm (about 20 psi). About 70 μg of the wet coating was applied. The wet coating was baked at about 140° C. for about 2 hours, yielding a dry primer layer.

A second composition was prepared by mixing the following components:

(a) about 2.0 mass % of EVAL;

(b) about 1.6 mass % of EVEROLIMUS; and

(c) the balance, DMAC solvent.

The second composition was applied onto the dried primer layer to form a drug-polymer layer, using the same spraying technique and equipment used for applying the primer layer. About 300 μg of the wet coating was applied, followed by drying, e.g., by baking as described above. The dry drug-polymer layer contained about 130 μg of EVEROLIMUS.

A third composition was prepared by mixing the following components:

(a) about 2 mass % of PBMA having M_n of about 154,000; and

(b) about 0.1 mass % of PEG having M_n of about 18,000; and

(c) the balance, a 1:1 by mass mixture of solvents, acetone and cyclohexanone.

The third composition was applied onto the dried drug-polymer layer, to form a topcoat layer, using the same spraying technique and equipment used for applying the primer and the drug-polymer layers. About 200 μg of the wet coating was applied, followed by drying, e.g., by baking as described above. The final amount of the dried topcoat was about 50 μg.

The kinetics of release of EVEROLIMUS in vitro was studied chromatographically (HPLC). To study the kinetics, three stents were coated as described above in this Example. The results of this study are illustrated by the chart shown by FIG. **4**. The amount of EVEROLIMUS released from a stent coating having the PBMA-PEG topcoat was measured (curve **1**). The average of the data obtained from the three stents was used to plot curve **1**. As a control, two identical control stents were used, except the topcoat included only pure PBMA instead of PBMA-PEG. The control curve **2** was plotted using the average of the data obtained from the two control stents. As seen from FIG. **4**, the rate of release of EVEROLIMUS through the PBMA-PEG topcoat is about twice the rate of release through the PBMA topcoat.

EXAMPLE 5

A primer and drug-polymer layers can be formed on a stent as described in Example 4, but instead of EVEROLIMUS, rapamycin can be used. A topcoat composition can then be prepared by mixing the following components:

(a) about 2 mass % of PBMA having M_n of about 154,000; and

(b) about 0.05 mass % of PEG having M_n of about 18,000;

(c) about 0.05 mass % of poly(propylene glycol) (PPG) having M_n of about 40,000; and

(c) the balance, a 1:1 by mass mixture of solvents, acetone and cyclohexanone.

If desired, poly(tetramethylene glycol) (PTMG) can be used in the topcoat composition instead of PPG. The M_n of PTMG can also be about 40,000. A PPG/PTMG blend having any ratio between PPG and PTMG can also be optionally used instead of PPG. In this example, in the topcoat composition the mass ratio between PEG and PPG is 1:1. If desired, the amount of PPG or PTMG, or a mixture thereof can be up to about twice amount of PEG. Optionally, all of the PEG in the topcoat composition can be replaced with PPG or PTMG, or with a mixture thereof.

The topcoat composition can be applied onto the dried drug-polymer layer, to form a topcoat layer, using the same spraying technique and equipment used for applying the primer and the drug-polymer layers. About 200 μg of the wet coating can be applied, followed by drying, e.g., by baking as described above. The final amount of the dried topcoat can be about 50 μg.

EXAMPLE 6

A primer and drug-polymer layers can be formed on a stent as described in Example 4. A topcoat composition can then be prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 1.9 mass % of poly(hexafluoropropene-co-vinylidene fluoride) (PHFP-VDF) having M_n about 125,000.

(b) between about 0.04 mass % and about 0.8 mass %, for example, about 0.1 mass % of F127 PLURONIC copolymer; and

(c) the balance, a mixture of solvents, the solvent mixture including acetone and cyclohexanone in a mass ratio of about 1:1.

F127 PLURONIC is a difunctional poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide)triblock copolymer terminating in primary hydroxyl groups. F127 PLURONIC has M_n of about 12,600.

The topcoat composition can be applied onto the dried drug-polymer layer, to form a topcoat layer, using the same spraying technique and equipment used for applying the primer and the drug-polymer layers. About 200 μg of the wet coating can be applied, followed by drying, e.g., by baking as described above. The final amount of the dried topcoat can be about 50 μg.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

What is claimed is:

1. An implantable medical device comprising a coating, the coating including

a mixture of at least one poly(meth)acrylate comprising a macromolecular chain and at least one polyalkylene glycol comprising a macromolecular chain,

wherein a physically entangled or interpenetrating system formed of the macromolecular chains of the poly(meth) acrylate and the polyalkylene glycol,

wherein the poly(meth)acrylate has a number average molecular weight (M_n) between about 50,000 and about 1,000,000 Daltons, and

wherein the polyalkylene glycol has a M_n between about 5,000 and about 100,000 Daltons.

2. The device of claim **1**, wherein the device is a stent.

3. The device of claim **1**, wherein a ratio between the poly(meth)acrylate and the polyalkylene glycol is between about 99:1 and about 9:1.

4. The device of claim **1**, wherein the poly(meth)acrylate is selected from a group consisting of poly(methyl methacrylate), poly(ethyl methacrylate), poly(n-propyl methacrylate), poly(iso-propyl methacrylate), poly(n-butyl methacrylate), poly(iso-butyl methacrylate), poly(tert-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(n-propyl acrylate), poly(iso-propyl acrylate), poly(n-butyl acrylate), poly(iso-butyl acrylate), and mixtures thereof.

5. The device of claim **1**, wherein the polyalkylene glycol is selected from a group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol), poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly (tetramethylene glycol), and mixtures thereof.

6. The device of claim **1**, wherein the coating additionally comprises a drug.

7. The device of claim **6**, wherein the drug is selected from a group consisting of rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, 40-O-tetrazole-rapamycin, and combinations thereof.

8. An implantable medical device comprising a coating, the coating including a mixture of at least one hydrophobic polymer comprising a macromolecular chain and at least one polymeric hydrophilic polymer comprising a macromolecular chain,

wherein a physically entangled or interpenetrating system formed of the macromolecular chains of the hydrophobic polymer and the hydrophilic polymer,

wherein the hydrophobic polymer has a number average molecular weight (M_n) between about 50,000 and about 1,000,000 Daltons, and

wherein the hydrophilic polymer has a M_n between about 5,000 and about 100,000 Daltons.

9. The device of claim **8**, wherein the device is a stent.

10. The device of claim **8**, wherein the hydrophobic polymer has a Hildebrand solubility parameter lower than about 10.7 $(cal/cm^3)^{1/2}$.

11. The device of claim **8**, wherein the hydrophobic polymer has an equilibrium water adsorption less than about 10 mass % at room temperature.

12. The device of claim **8**, wherein the hydrophobic polymer comprises poly(meth)acrylates, vinyl polymers, polyolefins, halogenanated polymers, polymers having urethane groups, polybutyrals, nylon, silicones, polycarbonate, or polysulfone.

13. The device of claim **12**, wherein the poly(meth) acrylates are selected from a group consisting of poly (methyl methacrylate), poly(ethyl methacrylate), poly(n-propyl methacrylate), poly(iso-propyl methacrylate), poly (n-butyl methacrylate), poly(iso-butyl methacrylate), poly (tert-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(n-propyl acrylate), poly(iso-propyl acrylate), poly(n-butyl acrylate), poly(iso-butyl acrylate), and mixtures thereof.

14. The device of claim **12**, wherein the vinyl polymers are selected from a group consisting of poly(ethylene-co-vinyl alcohol), poly(ethylene-co-vinyl acetate), poly(vinyl acetate), polystyrene, poly(styrene-co-iso-butylene), poly (styrene-co-ethylene-co-butylene-co-styrene) terpolymers, and poly(styrene-co-butadiene-co-styrene) terpolymers, and mixtures thereof.

15. The device of claim **12**, wherein the halogenanated polymers are selected from a group consisting of poly(vinyl fluoride), poly(vinylidene fluoride), polyhexafluoropropene, poly(hexafluoropropene-co-vinylidene fluoride), poly(ethylene-co-hexafluoropropene), polytetrafluoroethylene, poly (vinyl chloride), poly(vinylidene chloride), and mixtures thereof.

16. The device of claim **12**, wherein the polymers having urethane groups are selected from a group consisting of polyether urethanes, polyester urethanes, polyurethaneureas, polycarbonate urethanes, silicone urethanes, and mixtures thereof.

17. The device of claim **8**, wherein the polymeric hydrophilic compound is selected from a group consisting of polyalkylene glycols, hyaluronic acid, chondroitan sulfate, chitosan, glucosaminoglucans, dextran, dextrin, dextran sulfate, cellulose acetate, carboxymethyl cellulose, hydroxyethyl cellulose, cellulosics, polypeptides, poly(2-hydroxyethyl methacrylate), polyacrylamide, polyacrylimide, poly (ethylene amine), poly(allyl amine), poly(vinyl pyrrolidone), poly(vinyl alcohol), poly(acrylic acid), poly

(methacrylic acid), acrylic acid copolymers, methacrylic acid co-polymers, polyvinyl alkyl ethers, non-ionic tetrafunctional block-copolymer surfactants, gelatin, collagen, albumin, chitin, heparin, elastin, fibrin, and mixtures thereof.

18. The device of claim **17**, wherein the polyalkylene glycols are selected from a group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol), poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.

19. The device of claim **8**, wherein the ratio between the hydrophobic polymer and the polymeric hydrophilic additive is between about 99:1 and about 9:1.

20. The device of claim **8**, wherein the coating additionally comprises a drug.

21. The device of claim **20**, wherein the drug is selected from a group consisting of rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, 40-O-tetrazole-rapamycin, and combinations thereof.

22. An implantable medical device comprising a coating, the coating including a mixture of at least one hydrophobic polymer and at least one polymeric hydrophilic compound, wherein the macromolecular chains of the hydrophobic. polymer and the hydrophilic compound form a physically entangled or interpenetrating system, and

wherein the hydrophobic polymer comprises poly(meth) acrylates, vinyl polymers, atactic polypropylene, halogenanated polymers, polymers having urethane groups, polybutyrals, nylon, silicones, polycarbonate, or polysulfone.

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